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Clinical Similarities in Siblings With Schizophrenia

J.G. Burke, B.M. Murphy, J.C. Bray, D. Walsh, and K.S. Kendler

Department of Psychiatry, Faculty of Medicine, University of Leicester, Leicester, United Kingdom (J.G.B.); The Health Research Board, Dublin, Ireland (B.M.M., J.C.B., D.W.); Department of Psychiatry and Human Genetics, Medical College of Virginia, Richmond (K.S.K.), Virginia

Three symptom groups, identified by factor analysis of schizophrenic symptoms, together with other clinical variables, were compared among 80 sibships (169 individuals), containing two or more members affected with schizophrenia. The three factors, which were labelled negative symptom, disorganization, and reality distortion, all showed a moderate but significant degree of correlation between siblings. Age at onset was also significantly correlated. Such a familial pattern of clinical heterogeneity suggests underlying common familial aetiologies that influence the clinical form of the disorder. Whether these are genetic or environmental requires further investigation. This finding confers some external validation on the three factor model. It may be feasible to develop familial symptom patterns as the basis for an a priori approach to linkage heterogeneity.

KEY WORDS: familial psychosis, symptoms, factor analysis

INTRODUCTION

The genetic basis of schizophrenia is now well established [Kendler, 1988], but what remains uncertain is whether inherited elements have a direct influence on the clinical form of the disorder. A convenient means of examining this question is by comparing clinical features among affected relatives. Schizophrenia is considered to be an aetiologically heterogeneous disorder, but when cases cluster in a family, a single shared familial cause is likely. If a familial resemblance for clinical features is shown to occur, this would suggest that familial factors influence not only the general liability to develop schizophrenia but also the specific clinical features of the disorder.

There have been relatively few studies that examined the familial pattern of clinical variables in relatives diagnosed with schizophrenia. Many were conducted prior to the introduction of structured personal interviews and operationalized diagnostic criteria, and although very thorough and extensive, they can be difficult to interpret.

One approach utilized in recent studies has been to examine the concordance for classical Kraepelinian schizophrenic subtypes in families. It has yielded conflicting results. Of 12 relevant studies, five studies indicated a tendency for the subtypes to "breed true" within families and seven studies did not [Kendler and Davis, 1981; Ungvari, 1983; Kendler et al., 1988, 1994].

A second approach, which has been less frequently utilized, has been to examine familial similarities for specific clinical features in pairs of affected relatives. The findings have been inconsistent and a variety of clinical similarities have been reported over a number of studies: age at onset [DeLisi et al., 1987; Kendler et al., 1987; Gottesmann and Shields, 1972], premorbid personality [Bleuler, 1978], Kraepelinian subtypes [Gottesmann and Shields, 1972; Fischer, 1973], visual hallucinations [DeLisi et al., 1987] depression [DeLisi et al., 1987], course [Bleuler, 1978; Gottesmann and Shields, 1972], and outcome [Bleuler, 1978; Gottesmann and Shields, 1972].

The present study attempts to avoid methodological limitations, which detracted from previous studies, as follows: (1) a large sample of siblings with schizophrenia was collected, using operationalized criteria, thus ensuring relative diagnostic homogeneity, (2) siblings were selected, rather than other relative pairs, because being more likely to be at a similar point in their illness, their clinical features might be more validly comparable than other relative pairs, (3) symptoms were rates on a scale of severity, thereby achieving a more sensitive measure of symptomatology than previously reported, where the only measures of clinical symptoms were either clinical subtypes or the presence or absence of symptoms, and (4) factor analysis was performed on the schizophrenic symptoms to allow simplification of data, by reducing a large number of interrelated variables to a smaller number of clearly identifiable con-

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Address reprint requests to John G. Burke, Department of Psychiatry, Faculty of Medicine, University of Leicester, Clinical Sciences Building, Leicester Royal Infirmary, PO Box 65, Leicester LE2 7LX, UK.

structs. As reported in a previous work (which examined in detail the factor structure of schizophrenic symptoms in the same patient sample) [Murphy et al., 1994], this had yielded three factors.

In the present report, we examine familial resemblance for these factors, both among the sibships, and also between the individual sibling pairs, which in addition to its aetiological relevance would also provide some measure of external validation of the three factor model. As well as the factor pattern, we also investigate the familial distribution of other clinical variables, such as age at onset, affective symptoms, and outcome, which may provide additional insights into possible aetiological heterogeneity.

MATERIALS AND METHODS

Subjects

Sibships containing two or more members suffering from schizophrenia, as defined by DSM-III-R [APA, 1987], were identified during the course of a large genetic study in Ireland. The final sample contained a total of 169 siblings (110 males, 59 females) from 80 families. Of these, 71 sibships contained two affected siblings and nine contained three affected siblings. The 80 original sibships yielded 98 pairs using the "sib-pair method," as each sibship of three contained three possible pairs. There were 44 male pairs, 15 female pairs, and 39 opposite-sexed pairs. The mean age at evaluation was 44.8 yr, with a standard deviation of 14.1 and a range of 21–84 yr. The mean duration of illness was 19.9 yr, with a standard deviation of 11.6 and a range of 0–59 yr.

For each sibling, case notes were evaluated and interviews were conducted by three trained research psychiatrists (J.G.B., J.C.B., B.M.M.). For geographical reasons, members of each sibship were all interviewed by the same researcher. However, structured interviews were used to minimize bias. The assessment instruments consisted of modified sections of the Structured Clinical Interview for DSM-III-R [Spitzer et al., 1987] Axis I disorders (major depression, mania, cyclothymia, dysthymia, psychosis, alcohol use, panic disorder, and generalized anxiety disorder), including an expanded psychosis section. The scale for Assessment of Negative Symptoms [Andreasen, 1984] and the Levels of Functioning Scale [Strauss and Carpenter, 1972] were also included.

Diagnostic information on each individual was also reviewed blindly and independently (by both K.S.K. and D.W.), and the cases were included only when both reached diagnostic agreement.

Rating of Data

The material collected on each sibling was rated by separate researchers, and case note material was rated separately from interview material. Schizophrenic and affective symptoms were rated on a 5-point scale of severity: 1 = absent, 2 = possibly present but subthreshold, 3 = clearly present but moderate, 4 = clearly present and prominent, and 5 = very severe. Age at onset was estimated from earliest age of first clear prodromal or psychotic symptoms. Clinical outcome was measured on a 5-point scale of deterioration.

Interrater reliability was assessed by comparing the ratings of all three researchers on 15 cases. Interclass correlations derived from one-way random effects model, were above 0.8 for all items rated from interview. They were also above 0.8 for all items rated from case notes with the exception of delusions (0.76) and outcome (0.30).

Two separate sets of data were generated: clinical features rated from case notes and clinical features actually present at interview.

Data Analysis

Factor analysis was performed on the symptoms of schizophrenia from both sets of data. The following schizophrenic symptoms were included: affective flattening, inappropriate affect, catatonia, delusions, hallucinations, positive thought disorder (derailment, incoherence, etc.), and negative thought disorder (poverty of amount or content of speech). For interview data the global scores for avolition, anhedonia, and inattentiveness were also included (as affective flattening and negative thought disorder had already been rated).

Initial factors were extracted using the method of principal components. Orthogonal rotations were then performed by the method of VARIMAX and yielded three clear symptom groups [Murphy et al., 1994]. Factor 1 loaded heavily on negative thought disorder, affective flattening, anhedonia and avolition, and was labelled the negative symptom factor. Factor 2 loaded heavily on inappropriate affect and positive thought disorder and was labelled the disorganization factor. Factor 3 loaded heavily on hallucinations and delusions and was labelled the reality distortion factor.

For each factor in turn, one-way analysis of variance was used to compare the amount of variation of factor scores within the sibships to the amount of variation between the 80 sibships. As the factor scores were distributed nonnormally, and thus nonparametric tests were more appropriate, the Kruskal-Wallis test from the NPAR1WAY procedure of the Statistical Analysis System [SAS, 1990] was used and a Chi-square approximation was calculated to quantify the significance of the results. We assumed a one-tailed test of significance, as our a priori hypothesis was that siblings would resemble one another in their factor scores.

Spearman's correlation coefficient of factor scores between the 98 individual sibling pairs was calculated. To help correct for unreliability between raters, we calculated "corrections for unreliability" by dividing "raw" factor correlation scores by the corresponding interclass correlation coefficients. This method is similar to "corrections for attenuation" as described by Ferguson [1971].

The degree of sibling similarity for a number of other clinical variables was also studied. The intrapair correlations for age at onset were calculated by using Pearson's correlation coefficient. Intrapair correlations for the ratings of depressive symptoms, manic symptoms, and clinical outcome were calculated by using Spearman's correlation coefficient. The Chi-square test was used to analyze the degree of sex concordance.

TABLE I. Factor Score Distribution Among Sibships (Kruskal-Wallis One-Way Analysis of Variance)

	Case notes			Interview		
	Factor 1	Factor 2	Factor 3	Factor 1	Factor 2	Factor 3
Chi-square approximation	100.40	108.41	106.08	100.53	85.589	84.227
P value (79 D.F.)	0.026	0.008	0.011	0.025	0.143	0.161

TABLE II. Intrapair Correlations of Factor Scores

	Case notes			Interview		
	Factor 1	Factor 2	Factor 3	Factor 1	Factor 2	Factor 3
Raw correlations	* 0.226	** 0.299	*** 0.335	** 0.258	N.S. 0.127	N.S. 0.071
Corrections for unreliability	* 0.228	** 0.280	*** 0.447	** 0.261	N.S. 0.154	N.S. 0.079

* $P < 0.05$, ** $P < 0.01$, *** $P < 0.001$.

RESULTS

The Chi-square values derived from the Kruskal-Wallis test, together with their probability values, are detailed in Table I. Significant results occurred for all three factors. Only in the interview data did clearly nonsignificant results occur for the two positive factors (disorganization and reality distortion). Highly significant results occurred for the disorganization factor in case notes ($P = 0.008$). These results indicate a significant resemblance between members of the sibships for the three factors.

The correlation coefficients of the factor scores, between the individual pairs of siblings, and their significance levels are shown in Table II. The negative symptom factor showed moderately high correlations over both sets of data, especially interview data, where the correlation was highly significant. The disorganization factor showed highly significant correlations in data from case notes, but at interview correlations were weak and nonsignificant. The reality distortion factor was highly significantly correlated for data from case notes, but was not significantly correlated for interview data.

The resultant corrections for unreliability are detailed in Table II, where the greater degrees of correction reflect the greater unreliability between raters.

Correlation of the other clinical variables are presented in Table III. Age at onset showed a moderate but significantly positive intrapair correlation. Depressive symptoms failed to reach a significant level of correlation between siblings, and manic symptoms showed a moderate correlation in case notes only. There was a statistically significant but very weak correlation of clinical outcome in interview data.

Taking into account the large excess of male subjects in the sample, there was no significant abundance of male compared with female pairs, or of same-sexed compared with opposite-sexed (MM: observed = 44, expected = 41.1; MF: observed = 39, expected = 44.7; FF: observed = 15, expected = 12.1; Chi-square = 1.601, d.f. = 1, p = 0.206).

TABLE III. Intrapair Correlations of Other Clinical Variables†

	Case notes	Interview
Age at onset	** 0.259	** 0.242
Depressive symptoms	N.S. 0.127	N.S. 0.095
Manic symptoms	* 0.229	N.S. −0.014
Outcome		* 0.177

† Note: Outcome could not be reliably rated from case note data alone.
* $P < 0.05$, ** $P < 0.01$.

DISCUSSION

Factor Scores

A moderate but significant degree of resemblance, between affected siblings, has been shown for all three factors. This suggests that these symptom patterns are directly influenced by familial aetiological agents. Whether these are genetic or environmental in origin cannot be distinguished from the present data. As the intrapair correlations for each of the factor scores are quite similar, shared familial causes appear to underlie each symptom group to an equivalent degree.

The present demonstration of familial homogeneity in the overall context of wide clinical diversity suggests that a number of shared single familial causes may operate to underlie distinct familial clinical presentations. It thus offers some support for the contention that clinical heterogeneity may reflect aetiological heterogeneity.

The correlations of the factor scores vary, depending on which set of data was used. At interview, the only factor to correlate significantly was the negative symptom factor, which is as expected if negative symptoms are more enduring in nature and if positive symptoms vary in severity, being liable to be missed if the interview took place during a quiescent phase of the illness. Thus a better overview of the entire disease process is available from the case note data.

Age at Onset

The intrapair correlation obtained for age at onset was 0.242. Kendler et al. [1987], in a review of studies

of age at onset, showed a mean correlation of 0.68 for samples obtained by a method such as ours, where sibships with two or more schizophrenics are specifically sought and siblings with ages at onset closer together are more likely to be identified. An age correlation of 0.26 (very similar to ours) has been shown in the same review, for samples obtained by an alternative and more comprehensive method in which probands are ascertained systematically, independent of family history.

The similarity of our correlation to the latter figure substantiates the comprehensive nature of our ascertainment process, so that as well as the more clinically obvious sibling pairs (with ages at onset close together), others less readily identifiable were also included.

Affective Symptoms

Overall, affective symptoms showed little sibling resemblance. This contrasts with the findings of DeLisi et al. [1987] and is probably due to sample differences, as over half of their subjects had schizoaffective disorder, in contrast to the present homogeneous schizophrenic sample.

Interpreting Results

The degree of intrapair correlations achieved, although not very high in absolute terms, should be interpreted in the light of the fact that additive genetic factors correlate to a degree of 0.5 in first-degree relatives. In the present situation, where both relatives were selected because they have schizophrenia, the precise expected correlation is less clear, but likely to be even lower than 0.5.

Such a clinical resemblance among pairs of affected siblings would suggest that the underlying familial factors influence not only the general liability to develop schizophrenia, but also the specific liability to individual symptom patterns.

The present study is unable to clarify whether any correlation exists between the core vulnerability to develop schizophrenia and the liabilities to influence symptom patterns. If such a correlation were present, it would predict that the familial risk of schizophrenia would differ as a function of severity of symptom patterns. Current evidence from family studies fail to support this contention and would come closest to suggesting that clinical features, even though familially influenced, are not especially related to the vulnerability to schizophrenia and may reflect other aspects of cognitive organization.

An alternative explanation is of aetiologically independent conditions that breed true in families and that would result in no increased risk for a particular type in relatives of probands with another type. Recent family studies fail to support such a hypothesis [Kendler et al., 1994].

However, recent factor analytic studies suggest that the schizophrenic symptom groups, although not mutually exclusive, may result from different aetiological mechanisms. Associations have been shown between similar symptom patterns and specific neuropsychological deficits [Liddle, 1987] and also with altered perfusion at different cerebral loci [Liddle et al., 1992], suggesting that each symptom group is associated with a specific pattern of disordered brain function. The present study suggests that genetic factors or shared environmental causes may underlie these other mediating mechanisms.

Implications of the Results

One important application of these findings could be in linkage analysis, where standard a posteriori tests of linkage are relatively weak. Recently, in the case of two other complex non Mendelian disorders, i.e., familial breast cancer and Alzheimer's disease, a familial pattern of clinical heterogeneity has been demonstrated, which has proved useful as an a priori "predivided-sample" linkage test. In both disorders, evidence for linkage to polymorphic DNA markers has been demonstrated for an early onset subgroup, which was absent in the remainder [Hall et al., 1990; St. George-Hyslop et al., 1990].

It should be feasible to try to select high density families whose probands show similarities along the symptom dimensions that we have characterized, e.g., on the basis of whether they score high or low on a given trait. This could then be used to test whether there is heterogeneity of linkage, i.e., linkage occurring only within families where the schizophrenic patients on average had high versus low levels of a given symptom dimension.

In addition, such a demonstration of a familial pattern of clinical features may lead to a closer correlation of clinical heterogeneity with aetiological heterogeneity so that aetiologically meaningful subclassifications could be developed, which, as well as having possible implications for linkage analysis, would greatly improve our overall understanding of the nature of schizophrenia.

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